# Neuropsychology and Epilepsy

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## Factors Affecting Cognitive Function in Epilepsy

### What Seizure Related Factors May Affect Cognition in Epilepsy?

#### Seizure-Related Variables That May Affect Cognition and Behavior

- Some epilepsy syndromes are known to be associated with more adverse cognitive consequences than others.
  - Idiopathic Benign syndromes—e.g., BECTS (Rolandic), absence
  - Adverse syndromes—e.g., Lennox-Gastaut
  - Variable syndromes—Localization related epilepsies

#### Idiopathic Syndromes

- Less Education
- Decreased rates of employment
- Lower rates of marriage
- Poorer physical health
- Increased incidence of psychiatric disorders

#### Localization Related Syndromes

- Total and Segmented Volumes
  - (7.8 years vs. 23.3 years)

#### Total Lobar White Matter

- Cause or Effect?
  - Does white matter volume abnormality reflect neurodevelopmental
abnormality associated with early insult to developing brain?

- Does early lesion affect subsequent normal development of white matter connectivity?

### Age of Onset and Neuropsychological Outcome

<table>
<thead>
<tr>
<th></th>
<th>Early (7.8 yr)</th>
<th>Late (23.3 yr)</th>
<th>Healthy</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>37</td>
<td>16</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>90*</td>
<td>100</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Naming</td>
<td>47</td>
<td>52</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Verbal Mem</td>
<td>44</td>
<td>51</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>NV Mem</td>
<td>46</td>
<td>55</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>WCST PE</td>
<td>13</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

### Childhood TLE Onset

- Generalized cognitive compromise
- Reduction in cerebral volume, particularly white matter (~6-12%)
- Cerebral volume reduction not limited to temporal lobe
- Less focal impairment (e.g., memory)
- Less surgical risk
- Greater likelihood of functional reorganization (e.g., bilateral language, pathologic left handedness)

### Seizure-Related Variables That May Affect Cognition and Behavior

### Etiology

- Individuals with known causes for their epilepsy (e.g., head injuries, brain infections) typically have more detectable cognitive difficulties than those with no known etiology

### Seizure-Related Variables That May Affect Cognition and Behavior

### Seizure Burden

- Individuals with poorly controlled and severe seizures often have more detectable cognitive consequences than individuals with well-controlled and/or minor seizures

### Cumulative Seizure Effects?

(is epilepsy progressive?)

- Structural Imaging vs Behavior
- Cognitive and behavioral impairments present prior to treatment
- Newly diagnosed L TLE patients have verbal memory impairment

### Progressive Hippocampal Sclerosis

- Progressive hippocampal atrophy occurred only in patients with TLE and
continuing seizures
- n=12 unilateral TLE
- Repeat MRI=2.5-5.2 yr

23 \(\text{Hippocampal Volumes (mm}^2\text{)}\)

\begin{align*}
\text{Ipsi Volume} \\
\text{Sz Free (n=3)} & 2721 & 2733+12 \\
\text{Not SF (n=9)} & 2662 & 2391-271^* \\
\text{Contra Volume} \\
\text{Sz Free (n=3)} & 3697 & 3678-19 \\
\text{Not SF (n=9)} & 3717 & 3661-56
\end{align*}

24 \(\text{Neuropsychological Effects of Poorly Controlled Seizures}\)
- 20 longitudinal studies in children-adults
- 12/20 reported relationship/decline
- 5/20 mixed results
- 3/20 no relationship

25 \(\text{Neuropsychological Effects of Seizures}\)
- Decreased scores with higher number of seizures
- IQ lower with increased seizure frequency
- Greater performance “improvement” in controls than patients
- Losses seen beyond “memory”

26 \(\text{Cross-sectional TLE Neuropsychological Outcome}\)

27 \(\text{Educational Attainment and Seizure Duration}\)

28 \(\text{Progressive Decline?}\)
   - Verbal Learning vs. Vocabulary

29 \(\text{Memory Changes in TLE}\)
   - (2-10 years)

30 \(\text{Seizure-Related Variables That May Affect Cognition and Behavior}\)

31 \(\text{Transient Cognitive Impairment}\)
- Relationship of interictal EEG discharges to cognition (masked or larval epilepsy)

32 \(\text{Simple RT}\)

33 \(\text{Simple RT}\)

34 \(\text{Ictal Neglect}\)
Heilman & Howell, 1980: R P-O Sz with extinction; ictal Lt line bisect; R postictal
Feinberg et al., 1998: R F-T Sz with asomatognosia and alien hand
Thomas et al., 1998: R P-O Sz with anosognosia, asomatognosia and neglect on cancellation task
Meador & Moser (2001), s/p R ATL, neglect on cancellation and copy

35 ictal Neglect
43 yo RH man; sp right ATL
Interictal exam: mild memory impairment
Video EEG: multiple R centro-parietal Szs
Patient not aware of Szs
Left pronator drift, asterixis, & neglect
Hemi-inattention, hemi-dyslexia, anosognosia

36

37

38

39 Todd's Paralysis
Post-ictal focal neurologic deficit/weakness
Neuronal “exhaustion” from seizure
Resolves within minutes or hours

40 Postictal Language Assessment
Paraphasic errors
Time to speak following seizure
Inability to accurately read aloud “They heard him speak on the radio last night” within 60 sec after sz end
100% LTL Sz >68 sec to read correctly
98% RTL Sz <54 sec

41 Postictal vs Non-ictal Memory
(z scores)

<table>
<thead>
<tr>
<th>Pt</th>
<th>TLE</th>
<th>Verbal</th>
<th>VS</th>
<th>Laterality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R</td>
<td>+0.4</td>
<td>-2.1</td>
<td>+2.5</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>-0.9</td>
<td>-1.1</td>
<td>+0.2</td>
</tr>
<tr>
<td>3</td>
<td>R</td>
<td>-0.9</td>
<td>-1.8</td>
<td>+0.9</td>
</tr>
<tr>
<td>4</td>
<td>R</td>
<td>-2.9</td>
<td>-2.9</td>
<td>+0.0</td>
</tr>
<tr>
<td>5</td>
<td>L</td>
<td>-2.6</td>
<td>-1.5</td>
<td>-1.1</td>
</tr>
<tr>
<td>6</td>
<td>L</td>
<td>-2.4</td>
<td>-2.1</td>
<td>-0.3</td>
</tr>
<tr>
<td>7</td>
<td>L</td>
<td>-0.7</td>
<td>-0.4</td>
<td>-0.3</td>
</tr>
<tr>
<td>8</td>
<td>L</td>
<td>-2.6</td>
<td>+0.2</td>
<td>-2.7</td>
</tr>
</tbody>
</table>

42 Verbal Memory Scores Seizure
(max = 60)

<table>
<thead>
<tr>
<th>Control</th>
<th>L TLE</th>
<th>R TLE</th>
<th>Frontal</th>
</tr>
</thead>
</table>
43 V/S Memory Pre/Post Seizure (max = 36)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>LTLE</th>
<th>R TLE</th>
<th>Frontal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11</td>
<td>6</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Reorient</td>
<td>11</td>
<td>-2*</td>
<td>-8*</td>
<td>3</td>
</tr>
<tr>
<td>30 min</td>
<td>9</td>
<td>2</td>
<td>0*</td>
<td>0</td>
</tr>
<tr>
<td>60 min</td>
<td>12</td>
<td>7</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

44 Functional Plasticity
- Crowding - A decline in visual-spatial abilities associated with a shift in language dominance to the right cerebral hemisphere
- Decline in cognitive abilities occurs when "one hemisphere tries to do more than it had originally been meant to do"

45 “Crowding” in TLE

46 Language Localization

47 Factors Affecting Cognitive Function in Epilepsy

48 Phenobarbital (PB)
- Decreased IQ - improvement after PB discontinuation
- IQ changes - slowed mental growth rather than loss of previously acquired information or cognitive regression
- Decreased academic achievement
- Academic achievement impaired 3-5 years after PB discontinuation
  - Children do not fully "catch up"
- Concern for cumulative effects of other AEDs with milder cognitive side effect profile

49 Carbamazepine (CBZ)
- Increased (prolonged) RT
- Decreased EEG alpha rhythm (~ .5 Hz)
- EEG effect related to 1 year WISC-R performance
- Some children appear at disproportionate risk of cognitive decline

50 Older AEDs in Young Adults
- Neuropsychological impairment usually dose dependent
- May be individuals at unusual risk
- Memory and Quality of Life may be affected with serum concentrations in standard therapeutic range
Newer AEDs

- Clobazam
- Felbamate
- Fosphenytoin
- Gabapentin
- Lamotrigine
- Levetiracetam

- Oxcarbazepine
- Pregabalin
- Topiramate
- Tiagabine
- Vigabatrin
- Zonisamide

Can cause adverse cognitive side effects.
Newer AEDs typically have more favorable cognitive side effect profile but may still have some cognitive side effects
Of the newer AEDs, greater concern is for effect of topiramate (TPM, Topamax)
Side effects are typically dose dependent and greater when treated with more than one drug (polytherapy)

Children of Women with Epilepsy

- Majority of the children are normal
- As a group, both somatic & functional neurodevelopment are reduced
- Major Malformations
  - General population = 2 - 3%
  - Infants of mothers with epilepsy= 4 - 6% (R= 1.25 - 18.6%)

Prospective IQ Study

- 61% (182 / 300) children of epilepsy mothers
- 51% (141 / 278) control children
- IQ testing at mean age 7 y/o (2-10)
- **Verbal IQ**
  - VPA Monotherapy = 84 ± 3.8 SEM
  - CBZ Monotherapy = 96 ± 1.9
  - Healthy Control Group = 95 ± 1.2
- Controlled for age, education, & polytherapy
- CBZ=86, VPA=13, Other=8, PolyTx=30, None=45

Factors Affecting Cognitive Function in Epilepsy

- Non-seizure related factors that affect cognition
  - Developmental, neurological, psychiatric and medical disorders
  - Learning Disabilities
  - Developmental Disabilities
  - Mental Retardation

Non-seizure related factors that affect cognition

- Developmental, neurological, psychiatric and medical disorders
Psychosocial Status
- Mood
- Behavior
- Stigma

Comparison of Average Monthly Seizure Rate to HRQOL

Psychiatric Comorbidities

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy (range)</th>
<th>General Pop. (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11%–60%</td>
<td>2%–4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19%–45%</td>
<td>2.5%–6.5%</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2%–8%</td>
<td>0.5%–0.7%</td>
</tr>
</tbody>
</table>

Syndrome of Mesial Temporal Epilepsy
- Febrile seizure
- Early seizure onset
- Hippocampal sclerosis
- TLE seen without hippocampal sclerosis

Hemispheric Asymmetry
- Material-specific memory impairment
  - L TLE – Verbal more robust than R TLE - Nonverbal
- Confrontation naming impairment with Left TLE
- Age of seizure onset

Confrontation Naming
- Left TL volume related to BNT
- Left TL white matter and L hippocampal volume related to BNT
- Left TL white matter (not hippocampus) related to BNT recognition

BNT – L/R Cr/NA Ratios

Visual Naming vs. Auditory Naming

FDG-PET
Left TLE with MTS; normal MRI

Cognitive Impairment in TLE
- Decreased Full Scale IQ
- Diminished academic achievement
- Poor performance on WCST
• Diaschisis
• Nociferous cortex

70 MRI Volumetrics in Chronic TLE

• Generalized and diffuse cortical volume reduction
  • Ipsilateral hippocampus greatest
  • Ipsilateral & contralateral temporal, frontal, and parietal
• White matter > gray matter
  • Present with or without MTS
    (L=15, R=19, control=65)

71 Anterior Temporal Lobectomy

• Temporal lobe epilepsy most common CPS
• Verbal memory deficits – L medial TL onset
• Non-verbal memory impairment and R TLE less consistent
  • Related to age of seizure onset
  • Pathologic status of hippocampus

72 Surgery Variables

• “Standard” TL is not standard
  • Hippocampectomy vs ATL vs. ATL variations
  • Empiric vs. tailored resection
• ATL vs nonmesial TL vs. Extra TL resections vs. non-epilepsy variables (e.g., AVMs)

73 Cognitive Aging After ATL

(>9 yrs)

74 Memory, Aging, and Left TL Surgery

75 Goals of Wada Memory Testing

• Lateralize temporal lobe dysfunction
  • Assist in seizure onset lateralization
  • Identify risk for memory decline
    • Amnesia
    • Material-specific decline
• Goals emphasized to varying degrees among epilepsy centers

76 Models of Post-Operative Memory Decline

• Functional Reserve - Contralateral to focus
  • Traditional view, used for amnesia prediction
  • Wada memory following ipsilateral injection assesses assess memory capacity of contralateral TL
• Functional adequacy - Ipsilateral to focus
  • Wada memory following contralateral injection assesses memory capacity of TL to be resected

77 Wada Memory and
Memory Outcome

- Greatest verbal memory decline present in:
  - Left TLE patients who pass following Right Hemisphere injection (contralateral)
  - Left TLE patients who pass following Left Hemisphere injection (ipsilateral)
  - Patients without Wada memory asymmetries
  - Patients with reversed Wada memory asymmetries
- Poor to no relationship for non-verbal memory decline

Post-Surgical Memory Decline Risks

- Language dominant resection
- Absence of hippocampal atrophy/sclerosis
- Normal pre-op verbal memory performance
- Older seizure onset age
- Older age at surgery
- Functional assessments (e.g., Wada test) suggest greater residual preoperative function of the left temporal lobe

Functional Reserve: Patient AL

- Intracerebral EEG: bilaterally independent discharges, spike and slow wave activity (R>L)
- Seizures developed in R hippocampus and spread 2-3 seconds to L
- Subdural electrodes: 2 seizures began on R; 2 seizures with R rhythmic activity and simultaneous onset

Wada Results: Patient AL

<table>
<thead>
<tr>
<th>Left Injection</th>
<th>Right Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Early</td>
<td>8/8</td>
</tr>
<tr>
<td>Late</td>
<td>3/5</td>
</tr>
</tbody>
</table>

*Exclusive right cerebral language representation*

Memory Results: Patient AL

<table>
<thead>
<tr>
<th></th>
<th>Pre 5 mo</th>
<th>8 mo</th>
<th>38 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM I</td>
<td>15/50</td>
<td>4/50</td>
<td>3/50</td>
</tr>
<tr>
<td>LM II</td>
<td>3/50</td>
<td>0/50</td>
<td>0/50</td>
</tr>
<tr>
<td>VR I</td>
<td>38/41</td>
<td>34/41</td>
<td>35/41</td>
</tr>
<tr>
<td>VR II</td>
<td>34/41</td>
<td>5/41</td>
<td>6/41</td>
</tr>
</tbody>
</table>

*Post resection MRI revealed no evidence of L temporal abnormality*

Functional Adequacy: Patient MF

- 21 yo RH WM
- Simple, uncomplicated febrile seizure @ 9 mos
- Habitual seizures began at age 7 years
- Current seizure frequency of 2-3 per week
• Ictal and interictal EEGs revealed left temporal lobe seizure onset
• MRI revealed mesial temporal lobe sclerosis

83 Preoperative Results
• Full Scale IQ=110; VIQ=113, PIQ =106
• Delayed Auditory Memory Index=124
• Delayed Visual Memory Index=100
• Selective Reminding SS=112
• QOLIE-89 T = 47
• Wada testing
  • L inj= 8/8, 1 FP
  • R inj=8/8, 0 FPs

84 Outcome

85 Summary
• TL epilepsy associated with focal and generalized effects
• Long-term effects of seizures unclear
  • Earlier onset greater effect but less surgical risk
• Neuropsychology trumps anatomy in predicting outcome